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Composition for percutaneously administering metoclopramide

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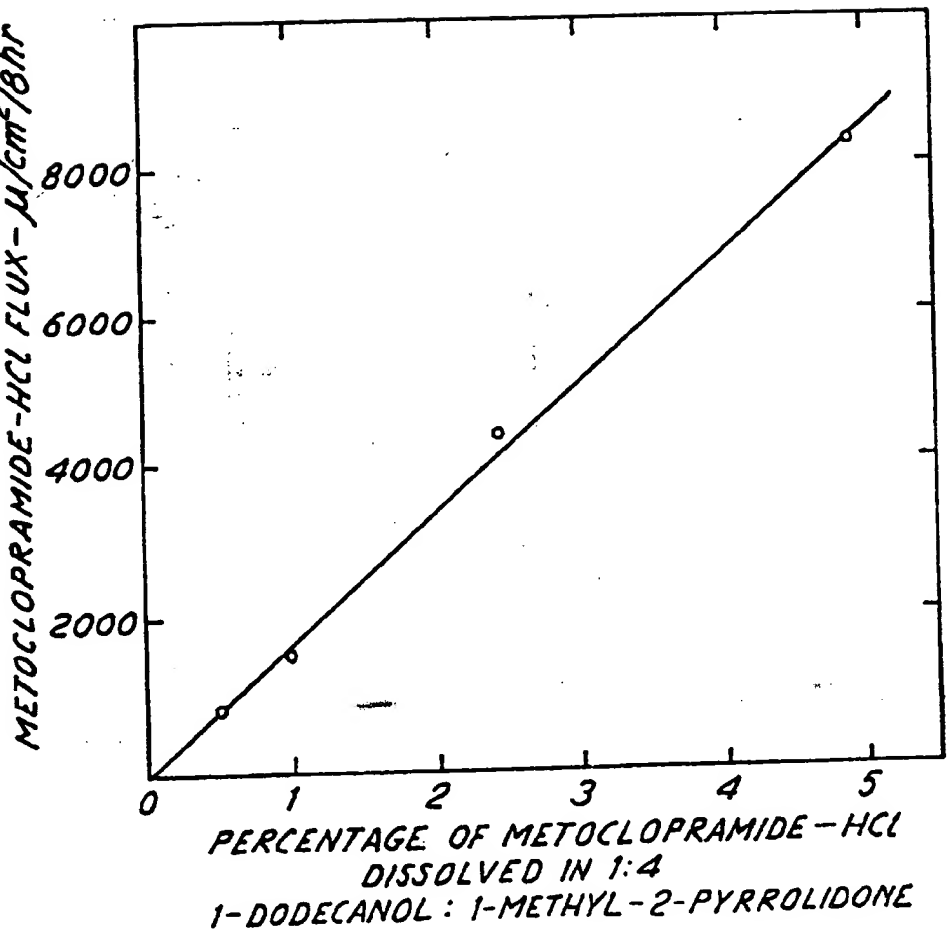

METOCLOPRAMIDE-HCl FLUX-μl/cm²/8hr
8000
6000
4000
2000
0
1
2
3
4
5
PERCENTAGE OF METOCLOPRAMIDE-HCl
DISSOLVED IN 1:4
1-DODECANOL : 1-METHYL-2-PYRROLIDONE

COMPOSITION FOR PERCUTANEOUSLY ADMINISTERING METOCLOPRAMIDE

The present invention relates to a method for accelerating the percutaneous absorption of metoclopramide (hereafter often merely referred to as MCP for brevity).

Drugs are commonly administered to the skin or mucosal tissues to treat local problems and systemic administration of drugs is commonly accomplished by ingesting pills or by injections. However, recently attempts have been made to achieve systemic administration of drugs by topical applications to the skin or mucosal tissues. Such topical means of achieving systemic administration has the advantage that desired blood levels can be readily achieved and maintained so that duration of therapy can be readily controlled. Thus, side effects due to an overdose of the drug can be prevented. Also, metabolism due to a first pass through the liver and gastric disturbances, which are characteristic of certain drugs such as indomethacin when administered orally, can also be prevented.

However, normal skin is relatively impermeable to most drugs, so that desired blood levels of the therapeutic agent cannot be achieved by means of percutaneous absorption. The percutaneous absorption of drugs can, however, be enhanced by means of adjuvants or penetration enhancers.

One of the best known of such penetrating adjuvants is dimethyl sulfoxide, the use of which is described in detail in U.S. Patent 3,551,554 (Herschler et al).

British Patent 1,504,302 (Brooker et al) deals with sedative methods and compositions and disclosures the administration of sedatives by applying to the skin of a non-human animal a sedating amount of one or more sedative compounds in various penetrating adjuvants such as hydrocarbons such as aromatic hydrocarbons or paraffins, halogenated aliphatic hydrocarbons, ketones, esters, ethers, alcohols, amides or sulfones.

U.S. Patent 4,202,888 (Eckert et al) discloses asorbable pharmaceutical compositions comprising at least one

cardiac glycoside distributed in a vehicle comprising an absorption-enhancing amount of at least a partial glyceride of a fatty acid of medium chain length.

U.S. Patent 3,472,931 (Stoughton) relates to percutaneous absorption using lower alkyl amides, and exemplifies binary systems which comprise dimethylacetamide and ethanol, dimethylacetamide and isopropyl alcohol and dimethylacetamide and isopropyl palmitate.

U.S. Patent 3,969,516 (Stoughton) discloses compositions for the treatment of acne which broadly can include "conventional formulating ingedients" including materials which enhance the percutaneous absorption of antibiotics of the lincomycin family, e.g., N-lower alkyl 2-pyrrolidones. Stearyl alcohol is used in the examples. This is a solid at 38°C and would be inoperable in the present invention.

U.S. Patent 3,989,816 (Rajadhyakshn) disloses percutaneous absorption systems for pyrrolidone-type compounds, including, e.g., in Example 3 isopropyl myristate, without any disclosure of the purpose of its inclusion. While stearyl and cetyl alcohol are disclosed, these are solids at 38°C and are inoperable in the present invention. Further, the pyrrolidone-type compounds used in the examples have a C_8 group corresponding to R_5 of the solvents of the present invention, which renders them useless in the present invention.

U.S. Patent 4,017,641 (DiGiulio) discloses skin moisturizing compositions (emulsions) containing 2-pyrrolidone. Stearyl and cetyl alcohol (solids at 38°C) are disclosed as useful components. DiGiulio also broadly discloses the use of certain esters of lanolin fatty acids, certain straight chain fatty alcohols or straight chain fatty alcohols.

European Patent Application 0043738 discloses binary percutaneous administration systems which comprise a monoglyceride, a diol or a diol ether in combination with a

second component such as an alcohol, ester, amide or the like.

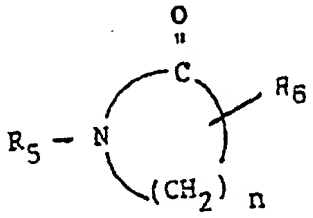
The present invention involves multicomponent carrier systems for the percutaneous administration of metoclopramide which differ from the systems disclosed in the above prior art.

In the present invention, it has been discovered that certain adjuvant-solvent systems provide enhanced and controlled percutaneous administration of metoclopramide (free base) and/or pharmaceutically acceptable salts thereof.

According to the invention we provide a pharmaceutical composition suitable for percutaneous administration, which comprises metoclopramide dissolved in a carrier system which comprises a mixture liquid at below 38°C, of

(a) at least one monovalent alcohol ester of an aliphatic monocarboxylic acid which ester has 8 to 32 carbon atoms, wherein the carboxylic acid moiety must have at least one unsaturated bond and/or at least one branched chain if the moiety has 18 or more carbon atoms, an alphatic monoalcohol having 6 to 24 carbon atoms and which must contain at least one unsaturated bond and/or at least one branched chain if it has 14 or more carbon atoms, or a mixture thereof, and

(b) at least one N-cyclic compound of the general formula



wherein R_5 represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms, R_6 represents an alkyl group having 1 to 4 carbon atoms and n is 3, 4 or 5.

We consider the N-cyclic compounds (b) to basically serve a solvent function and the esters and/or alcohols (a) to serve as adjuvants which enhance the solvating func-

tion of the solvent. We further believe that the solvents carry the active agent whereas the adjuvants open up the stratum corneum. We do not wish to be bound by these theories, and we merely use the terminology "solvent" and "adjuvant" to maintain a line of distinction between the two classes of materials which are used.

Mixtures of the esters and alcohols (a) may be used, as may mixtures of the N-cyclic type compounds (b). It is necessary that the alcohols, esters and pyrrolidone-type compounds have a melting point below 38°C, i.e., be liquid at 38°C. Of course, the final compositions of the present invention which are used for percutaneous administration must also be liquid at below 38°C.

In the present invention, metoclopramide can be percutaneously administered by blending it with the adjuvant(s) and solvent(s) and applying the mixture to the skin.

The above described composition can be used as bases for medical preparations comprising active agents applicable to the outer skin.

The composition of the present invention can enhance the percutaneous permeability absorption of metoclopramide, so that it can be administered in a rapid and controlled manner in man or other animals.

By application at appropriately adjusted rates, relatively constant therapeutic blood levels of metoclopramide can thus be obtained so as to avoid the side effects and reduced therapeutic effects that may result from wide fluctuations thereof in blood levels over time.

The adjuvants (a) used can be monovalent alcohol esters of aliphatic monocarboxylic acids having a total number of carbon atoms of from 8 to 32. (Diesters do not provide the results of the present invention). The esters are conveniently represented by the formula R_1COOR_2, R_1 representing the acid moiety and R_2 representing the alcohol moiety. The total number of carbon atoms in R_1 and R_2 can be from 7 to 31.

As the alcohol moiety, monovalent alcohols having 1 to 20 carbon atoms such as methyl alcohol, ethyl alcohol, n-propyl alcohol, isopropyl alcohol, n-butyl alcohol, iso-butyl alcohol, decyl alcohol, tetradecyl alcohol and oleyl alcohol are preferred. Further, as the monocarboxylic acid moiety, fatty acids having 2 to 20 carbon atoms are preferred and fatty acids having 2 or 8 to 18 carbon atoms are most preferred. Specific examples of such esters include methyl laurate, ethyl laurate, butyl laurate, isopropyl myristate, decyl oleate, myristyl acetate and cetyl acetate.

If the carboxylic acid moiety in the ester has 18 or more carbon atoms, the alcohol and/or carboxylic acid moiety must have at least one unsaturated bond and/or at least one branched chain to render the same liquid. In this situation it is preferred that the alcohol moiety have at least two carbon atoms, preferably more than two carbon atoms.

The presence of only one unsaturated bond is sufficient; the maximum number of unsaturated bonds is not limited. Similarly, the presence of only one branched methyl group is sufficient; the maximum number of carbon atoms in the branch(es) is not limited.

Higher aliphatic monoalcohols having from 6 to 24 carbon atoms may be branched, straight chain, saturated or unsaturated and may be primary, secondary or tertiary.

If the alcohol has 14 or more carbon atoms, it must contain at least one unsaturated bond and/or at least one branched chain to render the same liquid. The presence of only one unsaturated bond is sufficient; the maximum number unsaturated bonds is not limited. Similarly, the presence of only one branched methyl group is sufficient; the maximum number of carbon atoms in the branch(es) is not limited.

The solvents (b) are compounds represented by the general formula (I) as defined above. Examples of an alkyl group R_5 or R_6 which may be straight chain or branched are methyl, ethyl, n-propyl and iso-propyl. It is preferred

that n be 3 or 4, and it is most preferred that n be 3 since unexpectedly superior results are achieved (see Example 2).

Specific examples thereof include 2-pyrrolidone, N-methylpyrrolidone, N-methylpiperidone, caprolactam and N-methylcaprolactam.

It is mandatory that the adjuvant(s) and solvent(s) in the present invention both be present to achieve the synergistic effects of the present invention, as is shown by Example 8 herein below.

If desired, a C_3 to C_6 diol can be added to control (moderate) the rate of percutaneous metoclopramide administration, this is referred to herein as a "diol moderator". The diol can be straight or branched chain and the diol selected is preferably a diol comprising 3 to 6 carbon atoms.

The amount of any diol moderator used is not unduly limited, but is typically of the order of about 10 to about 400 weight percent, more preferably about 25 to about 200 weight percent, based on the weight of the solvent. The resulting combination of materials must, of course, be liquid.

The diol moderator reduces the activity of the adjuvant of the present invention and this provides a means of further controlling the rate of metoclopramide absorption.

Greater amounts of diol moderator decrease the rate of metoclopramide flux while lesser amounts of diol moderator increase the rate of metoclopramide flux as compared to greater amounts.

It is to be understood that the diol moderator does not enhance percutaneous absorption in the present invention, rather, in all amounts it reduces the rate of percutaneous absorption, which effect has not been hitherto suspected.

The compositions of the present invention may be prepared by dissolving the metoclopramide in the adjuvant or solvent or mixture thereof, and then mixing the diol moderator therein if it is used. The order of mixing is

not important. The amount of adjuvant used is generally from 0.5 to 95% by weight based on the total weight of adjuvant plus solvent plus metoclopramide, preferably 1 to 90% by weight same basis, the amount of solvent used being, accordingly, from 99.5 to 5% by weight, preferably 99 to 10% by weight, same basis. Preferred proportions of diol moderator have earlier been given. Of course, pharmaceutically acceptable additive such as water, etc., can also be added to the base compositions.

The amount of metoclopramide blended is sufficient if it is effective for achieving the desired pharmaceutical effect, which varies depending upon the body weight of the patient, symptoms, etc. The amount may thus be suitably chosen depending upon these conditions. In general, it is preferred that metoclopramide be employed in an amount of 0.1 to 60% by weight, more preferably 0.5 to 35% by weight, based on the weight of adjuvant plus solvent.

The dose of the metoclopramide administered can be controlled by increasing or decreasing the area of skin to which the pharmaceutical compositions are applied. Accordingly, the amount thereof is not necessarily limited to the above described amounts.

In the accompanying drawing:

the figure shows the effect of increasing the concentration of the metoclopramide HCl in a mixture of 25% 1-dodecanol and 1-methyl-2-pyrrolidone on the metoclopramide flux.

As will be apparent, with increasing concentrations of metoclopramide increasing amounts thereof will be absorbed by the subject. The following discussion is given in terms of blood levels of drug (ng/ml of plasma), this being dependent upon the total area of dermal application, as there is a substantially linear increase in amount of active agent absorbed with area.

For a constant area of application and a constant absolute amount of adjuvent, the blood level of metoclopramide at any given time is a function of the concentration of the same in the composition. That is, increased concen-

trations of metoclopramide in the formulation result in more rapid metoclopramide penetration and higher blood levels.

A further factor which must be considered is that the amount of metoclopramide absorbed will depend on the site of application, for example, scalp, ventral forearm, behind the ear, chest, etc. Typically an area rich in blood vessels is selected.

For most applications, the amount of metoclopramide applied will be about 0.1 to 100 mg per cm^2 and the total area of application will be of the order of about 0.5 cm^2 to about 100 cm^2, which will provide therapeutic blood levels of the metoclopramide. These ranges are not, however, limitative.

In general, the rate of transepidermal metoclopramide absorption will approach the rate of oral absorption depending upon the factors previously discussed (nature and amount of adjuvent and solvent, concentration of metoclopramide in the formulation, and surface area of skin application). Thus, peak blood levels of the metoclopramide may be reached more slowly or at about the same rate and will reach about the same level as those obtained by oral administration. Alternatively, the blood levels of metoclopramide attained by single dose intravenous administration may be maintained for an extended period by subsequent percutaneous administration of the metoclopramide. In the latter case, the initial i.v. dose may be smaller than the normal therapeutic i.v. dose so that side effects associated with the higher-than-minimal therapeutic blood levels attained by a reduced i.v. dose may be maintained by the subsequent transepidermal administration at a proper rate.

The method of the present invention finds application with mammals in general, most particularly man and domestic animals such as cows, sheep, horses, dogs and cats.

The pharmaceutical composition of the present invention is administered to the outer skin as a simple mixture or as a medical preparation by adding known pharmaceutically

acceptable third components in the form of solutions, ointments (paste-including creams and gels), lotions, adhesive tapes, a plaster, etc.

For example, solutions may simply comprise metoclopramide agent dissolved in the adjuvant and solvent with optional components, e.g., glycerin, etc,. and the solutions may be incorporated into absorbants, e.g. gauze, or a porous membrane, etc.

Ointments, gels or creams may contain conventional ingredients (e.g., polyethylene oxide) to form the same, and the same may be spread onto backing materials, e.g. a plastic film.

Similarly, plasters or adhesives tapes may contain the metoclopramide, adjuvent and solvent in an adhesive base, e.g., acrylic copolymers or other synthetic gums.

In a further preferred form of the invention a cellulosic gelling agent is present, typically a hydroxyalkylcellulose, e.g., hydroxyethylcellulose, hydroxyproylcellulose, hydroxypropylmethylcellulose, etc., generally in an amount of 1 to 10 wt% based on the weight of adjuvant plus solvent. The resulting gel is conveniently carried on a support.

The above listed components should essentially be inert in the system and not increase the effect of the adjuvant.

In developing the present invention, we used both diffusion cells and an animal model. The diffusion cell methods provided a qualitative assessment of the metoclopramide/adjuvant effect on percutaneous absorption. The animal model rhesus monkey test also provides an acceptable pharmacokinetic model for man as indicated in J. Soc. Cosmet Chem., 30, 297-307. Sept./Oct. 1979 and Toxicol. Appl. Pharmacol., 32, 394-398, 1975.

Hereafter, metoclopramide is generally referred to as "MCP". Examples of useful pharmaceutically acceptable salts include the HCl or di HCl salts, etc.

EXPERIMENTAL

In Vitro Skin Penetration Studies with Diffusion Cell Technique

Rat full thickness skins were used in the diffusion cell method of Michaels, AIChE Journal, 21 [5], 985-996 (1975). The rat skin was mounted in the diffusion cell in a vertical position between the upstream and the downstream compartments; the exposed area of the skin approximated 4.15 cm^2.

The skin was excised from the shaved abdominal site of male albino rats weighing 250 - 300 g, and washed with normal saline solution after the subcutaneous fat was carefully removed with scissors.

An MCP solution of known concentration was added to the upper compartment of the cell, which was exposed to the epithelial side of the skin and a normal saline solution was placed in the lower compartment.

The penetration rate was studied in a thermostated bath at 30°C. At appropriate intervals samples were withdrawn from the lower compartment and subsequently analyzed for MCP concentration by standard analytical methods. This procedure was used in Examples 1 to 10.

In Vivo Rhesus Monkey Test

Male rhesus monkeys weighing 8-14 Kg were used as the subject. An appropriate area of the monkey's chest was shaved 24 hours before drug application.

MCP HCl formulations were applied to a certain area of the chest. The monkey was restrained in a chair to prevent it from touching its chest.

Blood samples were taken at appropriate intervals after the application. The heparinized blood was centrifuged, and the plasma removed and stored at -20°C until analyzed.

MCP was analyzed following the HPLC method of Graffner, Lagerstrom and Lundborg, Br. J. Clin. Pharmac. 8, 469-474 (1979). The results are set forth in the following examples.

This test was used in Examples 12 to 15 and MCP was analyzed per the Graffner et al method in control Example 11.

Further in the following examples, the abbreviations below are used:

$C_{12}OH$ - 1-dodecanol
MP - 1-methyl-2-pyrrolidone
PG - 1,2-propanediol

Unless otherwise indicated, in all of the examples the active agent was MCP·HCl, the MCP·HCl flux is given in terms of ug/cm²/8hrs, 25 volume percent of the adjuvant with respect to the adjuvant plus solvent volume was used in combination with 2.5 weight percent of active agent based on the weight of the adjuvant plus solvent; otherwise, all percentages are by volume based on adjuvant, solvent or adjuvant plus solvent volume, depending on the system.

Compositions were prepared by merely mixing the adjuvant and solvent together, then mixing the MCP·HCl in the mixture and then, if used, mixing the diol therein. The order of mixing is not important.

Example 1

This example shows the flux of MCP·HCl with combinations of various alcohols and 1-methyl-2-pyrrolidone.

Alcohol	MCP·HCl Flux(µg/cm²/8hrs)
1-Octanol	3834
4-Octanol	3176
Linalol	4066
Dracosantol	2163
1-Dodecanol	4552
Oleyl Alcohol	3287
2-Octyl-1-Dodecanol	2176
Phytol	3040
2-Decyl-1-Tetradecanol	1410

Example 2

This example shows the use of 1-dodecanol as the adjuvant in combination with various pyrrolidone-type compounds as solvents. MCP·HCl was used as the active agent.

Combination	MCP·HCl Flux(μg/cm²/8hrs)
25% $C_{12}OH$ in 2-Pyrrolidone	2511
25% $C_{12}OH$ in 1-Methyl-2-pyrrolidone	4552
25% " in 1-Ethyl-2-pyrrolidone	2841
25% " in 1-Butyl-2-pyrrolidone	2029
25% " in 1,5-Dimethyl-2-pyrrolidone	1533
25% " in 1-Methyl-2-piperidone	4031
25% " in 1-Methyl-caprolactam	2693

Example 3

This example shows the relative MCP·HCl flux with lower concentration of $C_{12}OH$ in MP compared to the flux with 25% $C_{12}OH$ in MP.

Combination	Relative Flux
25% $C_{12}OH$ in MP	as 1.0
10% $C_{12}OH$ in MP	1.0
5% $C_{12}OH$ in MP	0.7
1% $C_{12}OH$ in MP	0.6
0% $C_{12}OH$ in MP (MP alone)	0.1

Example 4

This example shows the use of MP as a solvent in combination with various esters as adjuvants and also with myristyl myristate (solid at 38°C) as a comparison study.

Combination	MCP·HCl Flux(μg/cm²/8hrs)
25% Ethyl Caprylate in MP	2793
25% Decyl Oleate in MP	2678
25% Myristyl Myristate in MP	117

Example 5

This example shows comparisons of the relative flux of MCP (free base) and its HCl salt with 25% $C_{12}OH$ in MP and 25% isopropyl myristate in MP.

Formulation		Relative Flux
25% 1-Dodecanol in MP	: Free base	as 1.0
	: HCl Salt	1.3
25% isopropyl myristate	: Free base	1.0
	: HCl Salt	1.2

Example 6

This example shows the effect of increasing the MCP HCl concentration in a 25% $C_{12}OH$ in MP combination on MCP HCl flux. Flux increases linearly with increasing drug concentration, as shown in the results plotted in the accompanying drawing.

Example 7

This example shows the moderating effect of a diol on the system 25% $C_{12}OH$ in MP and the system 25% decyl oleate in MP.

Formulation	Relative Flux
25% $C_{12}OH$ in MP	as 1.00
25% $C_{12}OH$ in a 1/1 volume mixture of MP/1,2-Propanediol	0.30
25% Decyl Oleate in MP	as 1.00
25% Decyl Oleate in a 1/1 volume mixture of MP/1,2-Propanediol	0.25

Example 8

This example shows the MCP·HCl flux with various concentration of $C_{12}OH$ in a 1:1 volume mixture of MP : 1,2-propanediol.

Formulation	Relative Flux
$C_{12}OH$ alone	0.1
75% $C_{12}OH$ in MP/1,2-Propanediol	1.7
50% $C_{12}OH$ in MP/1,2-Propanediol	1.3
25% $C_{12}OH$ in MP/1,2-Propanediol	as 1.0
10% $C_{12}OH$ in MP/1,2-Propanediol	1.0
MP/1,2-Propanediol alone	0.0

Example 9

This example shows the moderating effect of a diol on the system 25% $C_{12}OH$ in MP along with 2.23 weight percent of MCP (free base).

Formulation	Relative Flux as
25% $C_{12}OH$ in MP	1.00
25% $C_{12}OH$ in MP/2,3-Butanediol=1/1	0.35
25% $C_{12}OH$ in 2,3-Butanediol	0.05

Example 10

500 mg of MCP·HCl was dissolved in 20 ml of 10% $C_{12}OH$ in MP. A 5 ml sample of the solution was added to 300 mg of hydroxy propyl cellulose (Klucel HF, Hercules Inc.) and to 300 mg of hydroxy ethyl cellulose (Natrosal 250H, Hercules Inc.). Uniform gel formulations were obtained. These formulations were added to diffusion cells and the MCP·HCl flux for 8 hours was measured.

Formulation	MCP·HCl Flux($\mu g/cm^2$/8hrs)
Hydroxy ethyl cellulose	1296
Hydroxy propyl cellulose	843

Example 11

This control study shows the *in vivo* MCP·HCl plasma level in a rhesus monkey after oral administration of MCP·HCl (Reglan Tab., A.H. Robins Co.) and intravenous injection thereof (Reglan Injectable, A.H. Robins Co.).

20 mg Oral Administration:

Time after application	30'	1hr	2hrs	3hrs.	5hrs	7hrs
MCP·HCl plasma level (ng/ml)	8	19	7	5	5	3

Intravenous Injection

Time after application		10'	20'	40'	60'	90'	2hrs	3hrs	5hrs	7hrs
Plasma level (ng/ml)	5 mg injec.	169	122	117	87	65	61	32	17	10
	10mg "	378	162	193	--	148	93	45	40	28

Example 12

This example shows the *in vivo* MCP·HCl plasma level in a rhesus monkey resulting from the use of a topical gel formation of MCP·HCl as described below. 150 mg of MCP·HCl was dissolved in 3 ml of $C_{12}OH$ in MP. To this solution was added 90 mg of Klucel (type HF). A uniform

gel was obtained. 0.5 ml of the gel was placed in a polyester cup having 4 cm^2 opening and a volume of 0.5 ml. The gel in the cup was applied on the monkey chest as earlier described.

Time after application	1hr	3hrs	7hrs
Plasma level (ng/ml)	117	65	72

Example 13

This example shows the in vivo MCP·HCl plasma level obtained in a rhesus monkey with a topical gel formulation as described below. 200 mg of MCP·HCl was dissolved in 4 ml of 25% decyl oleate in MP. To this solution was added 160 mg of Klucel (type HF) and the system was stirred thoroughly to obtain a uniform gel. 1.0 ml of the gel was applied to a 49 cm^2 chest area of a rhesus monkey and the applied area was open to the air for the duration of the experiment.

(ng/ml of Plasma)

1 hr	2 hrs	3 hrs	5 hrs	7 hrs
5	13	23	32	22

Example 14

200 mg MCP·HCl was dissolved in 4 ml of 25% $C_{12}OH$ in 1/1 volume mixture of MP/1,2-propanediol. To this solution was added 1.2 g of polyvinyl pyrrolidone K-90 (molecular weight: 36,000) and the system stirred to obtain a viscous solution. 0.5 ml of this solution was placed in a polyester cup having a 4 cm^2 opening and a volume of 0.5 ml. The solution in the cup was applied to the chest of a rhesus monkey and attached thereto with adhesive.

(ng/ml of Plasma)

1 hr	3 hrs	7 hrs
5	10	20

Example 15

200 mg of MCP·HCl was dissolved in 4 ml of 10% $C_{12}OH$

in a 1/1 volume mixture of MP/1,2-propanediol. To this solution was added 160 mg of Klucel and the system stirred to obtain a uniform gel. 1.0 ml of the gel was applied to a 49 cm^2 area on the rhesus monkey chest and the applied area was left open to the air.

ng/ml of Plasma

1 hr	2 hrs	3 hrs	5 hrs	7 hrs
75	146	178	121	93

The term "Klucel" used in Examples 10, 12, 13 and 15 is a registered Trade Mark.

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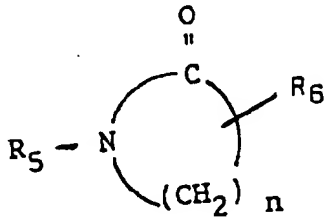
CLAIMS

1. A pharmaceutical composition suitable for percutaneous administration, which comprises metoclopramide dissolved in a carrier system which comprises a mixture liquid at below 38°C, of

(a) at least one monovalent alcohol ester of an aliphatic monocarboxylic acid which ester has 8 to 32 carbon atoms, wherein the carboxylic acid moiety must have at least one unsaturated bond and/or at least one branched chain if the moiety has 18 or more carbon atoms, an alphatic monoalcohol having 6 to 24 carbon atoms and which must contain at least one unsaturated bond and/or at least one branched chain if it has 14 or more carbon atoms, or a mixture thereof, and

(b) at least one N-cyclic compound of the general formula



wherein R_5 represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms, R_6 represents an alkyl group having 1 to 4 carbon atoms and n is 3, 4 or 5.

2. A composition as claimed in Claim 1, wherein the liquid mixture comprises 0.5 to 95 weight% of component (a) and 99.5 to 5 weight% of component (b).

3. A composition as claimed in Claim 1 or 2, wherein in an ester (a) the acid moiety has 2 to 20 carbon atoms.

4. A composition as claimed in Claim 3, wherein the acid moiety has 8 to 18 C atoms.

5. A composition as claimed in any preceding claim, which also includes a diol having 3 to 6 carbon atoms.

6. A composition as claimed in Claim 5, wherein the diol is present in an amount of 10 to 400 weight percent of the component (b).

7. A composition as claimed in any preceding claim, together with additional carrier components to form a solution, ointment, lotion, adhesive tape, or incorporated into an absorbent vehicle.

8. A pharmaceutical composition as claimed in Claim 1, substantially as hereinbefore described with reference to any of the foregoing Examples.